REMARKS

Reconsideration of this application is respectfully requested. The specification has been amended to remove the incorporation by reference of a European publication. The phrases "an analogues thereof," "cellulose derivatives," "silica acid or a derivative or salt thereof," and "phthalate derivatives" have been removed from claims 1, 27, 28, 41, 51, and 56. Claim 2 has been canceled without prejudice. Claim 41 has been amended to remove the transitional phrase "including." Claim 42 has been amended to recite that at most 10% w/w of the active ingredient is released within the first 3 hours following administration. *See* page 21, line 32, to page 22, line 2, of the specification. No new matter has been added by these amendments. Claims 1, 3–29, 31–34, 36–44 and 51–56 are pending. As claims 12, 38 and 39 have been withdrawn from consideration, claims 1, 3–11, 13–29, 31–34, 36, 37, 40–44 and 51–56 are currently at issue.

Objection to the Specification

The specification has been objected to for incorporating by reference a European publication. The specification has been amended to remove this incorporation by reference. Accordingly, applicants respectfully request withdrawal of this objection.

Indefiniteness Rejections

Claims 1, 3–11, 13–37, 40–44 and 51 have been rejected as indefinite. Specifically, claims 1, 22–23, 7, 37 and 44 have been rejected for including the terms "between about," "from about," and "at least about." The Examiner argues that it is unclear as to what range is covered because it is unclear whether "between," "at least," "from," or "about" controls the metes and bounds of the respective phrases.

The courts have indicated that the term "about" at the end of a range is definite. For example, in *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983), the

Court of Appeals for the Federal Circuit held that "a limitation defining the stretch rate of plastic as 'exceeding about 10% per second' is definite because infringement could clearly be assessed through the use of a stopwatch." Similarly, here the weight percentages recited in the claims can be clearly assessed using techniques and equipment in the art, such as scales. Applicants also respectfully point out that the Patent Office has issued tens of thousands of patents with each of the phrases "between about," "from about," and "at least about" in the claims, as shown by Exhibit A.

Claim 41 has been rejected for reciting the transitional phrase "including" in a Markush group. Claim 41 has been amended to delete this phrase.

Claim 42 has been rejected since the claim does not recite what is released. Claim 42 has been amended to recite that at most 10% w/w of the active ingredient is released within the first 3 hours following administration. *See* page 21, line 32, to page 22, line 2, of the specification.

Written Description Rejection

Claims 1, 3–11, 13–29, 31–34, 36, 37, 40–44, 51, 53, 55 and 56 are rejected as lacking written description due to the phrase "free of organic solvent." The Examiner argues that the specification does not provide support for a composition "free of organic solvent."

The specification teaches that solid dispersions are within the scope of the invention, and that the solid dispersions can be obtained by either using an organic solvent or another suitable medium (see p. 24, lines 34-36). Additionally, p. 25 of the specification teaches that "solid dispersions (solvent method) are prepared by dissolving a physical mixture of the active substance (e.g., a drug substance) and the vehicle or carrier in a common organic solvent, followed by evaporation of the solvent." One of ordinary skill in the art would have immediately recognized that evaporation of the solvent means that the solvent is no longer present, i.e., the composition is free of organic solvent. Additionally, one of ordinary skill in the art would have known that a solid dispersion using "another suitable medium [besides an organic solvent]" would exclude an organic solvent (see p. 23, ll. 34–36).

Claims 1, 3–11, 13–37, 40–44 and 51 have been rejected as lacking written description due to the phrases "analogues thereof," "cellulose derivatives," "silica acid or a derivative or salt thereof," and "phthalate derivatives." [JPL – START HERE] While applicants respectfully disagree with the Examiner, these terms have been removed from the claims in order to expedite prosecution.

Obviousness Rejection – U.S. 2003/0180352 (Patel)

Claims 1, 3–11, 13–29, 31–34, 36, 37, 40–44 and 51–56 are rejected as obvious over Patel. The Examiner contends that Patel teaches a solid dosage formulation of tacrolimus, PEG-24 cholesterol ether (Solulan C-24), distilled monoglycerides, and deoxycholic acid, coated on nonpareil seeds. *See* Example 20 of Patel. According to the Examiner, Patel discloses that the formulation may include other additives, such as polyethylene glycol 6000 (PEG 6000) and poloxamer.

Patel does not disclose or suggest a composition comprising tacrolimus, PEG and poloxamer. Patel provides an extremely broad description of solid pharmaceutical compositions encompassed by his invention:

> In one embodiment, the solid pharmaceutical composition includes a solid carrier, the solid carrier including a substrate and an encapsulation coat on the substrate. The encapsulation coat includes at least one ionic or non-ionic hydrophilic surfactant. Optionally, the encapsulation coat can include an active ingredient, a lipophilic component such as a lipophilic surfactant or a triglyceride, or both an active ingredient and a lipophilic component.

(Patel, ¶0031). Hundreds of active ingredients are listed (Patel, ¶0051-0141). Hundreds of suitable surfactants are listed (Patel, ¶0143-212). Numerous other possible components are also listed (Patel, ¶213-270). While poloxamer and PEG are individually listed as possible components, Patel does not provide any motivation to specifically combine these two components from the tens of thousands of possible combinations of components. Of the 36 exemplified formulations in Patel,

none includes poloxamer and PEG. Accordingly, a skilled artisan would not have been motivated to prepare a formulation containing tacrolimus, poloxamer, and PEG.

Furthermore, the presently claimed tacrolimus composition provides significantly superior bioavailability compared to a marketed form of tacrolimus known as Prograf®. *See* Example 6 (pages 35 and 36) of the specification. The formulation of the present invention exhibited an area under the curve (AUC) that was more than 7 times that obtained with Prograf®, despite the fact that both formulations contained the same amount of tacrolimus. Patel does not disclose or suggest that the presently claimed formulation would exhibit such a significant enhancement in bioavailability.

In *KSR v. Teleflex*, the Supreme Court held that "a factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning." *KSR v. Teleflex*, 550 U.S. 398 (2007). The Examiner's reasoning appears to fall into the area that the *KSR* court explicitly warned against. Only with hindsight knowledge that a tacrolimus composition can be formulated with PEG and poloxamer and exhibit significantly enhanced bioavailability, can the Examiner argue that it would have been obvious to select these particular components for a dosage form, from the thousands of possible combinations that could be derived from the teachings of Patel.

For the foregoing reasons, Patel does not render obvious the presently claimed invention. Accordingly, applicants respectfully request withdrawal of this rejection.

Double Patenting Rejections

Claims 1, 3–11, 13–29, 31–34, 36, 37, 40–44 and 51–56 are provisionally rejected for obviousness–type double patenting over claims 1, 6–12, 17–23, 26–32, 34–37, 63 and 64 of copending application 10/513,807. Claims 1, 3–11, 13–29, 31–34, 36, 37, 40–44 and 51–56 are provisionally rejected for obviousness–type double patenting over claims 1–50 of copending application 11/885,992. Applicants request that these provisional rejections in abeyance until a claim is found allowable.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

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